A randomized trial of the effect of estrogen and testosterone on economic behavior

Niklas Zethraeus[a], Ljiljana Kocoska-Maras[b], Tore Ellingsen[a], Bo von Schoultz[b], Angelica Lindén Hirschberg[b], and Magnus Johannesson[a,1]

[a]Department of Economics, Stockholm School of Economics, Box 6501, SE-113 83 Stockholm, Sweden; and [b]Department of Woman and Child Health, Division of Obstetrics and Gynecology, Karolinska Institutet, SE-171 77 Stockholm, Sweden

Edited by George A. Akerlof, University of California, Berkeley, CA, and approved February 17, 2009 (received for review December 15, 2008)

Existing correlative evidence suggests that sex hormones may affect economic behavior such as risk taking and reciprocal fairness. To test this hypothesis we conducted a double-blind randomized study. Two-hundred healthy postmenopausal women aged 50–65 years were randomly allocated to 4 weeks of treatment with estrogen, testosterone, or placebo. At the end of the treatment period, the subjects participated in a series of economic experiments that measure altruism, reciprocal fairness, trust, trustworthiness, and risk attitudes. There was no significant effect of estrogen or testosterone on any of the studied behaviors.

sex hormones | trust game | ultimatum game | risk aversion

Humans display sizeable individual variation in economic behaviors. Heterogeneity is large both in the domain of personal decision making and in the domain of social interaction. Some individuals willingly take risks that others pay to avoid (1), and in situations where some individuals are altruistic and trusting, others are selfish and distrustful (2).

Relatively little is known about the sources of such preference heterogeneity, but two recent findings suggest that biological factors are important. First, comparisons of the behavior of identical and fraternal twins indicate that genetics explains a sizeable part of the variation in preferences across a wide range of economic domains (3–5). Second, a controlled increase in the level of the mammalian hormone oxytocin causes more trusting behavior (6).

Several studies also report that behavior is correlated with the level of sex hormones. Burnham (7) finds that subjects with a higher testosterone level are more likely to reject unfair offers in the ultimatum game, and Apicella et al. (8) find a correlation between testosterone levels and financial risk-taking behavior. Two studies report that risk-taking behavior varies over the menstrual cycle; women are more risk averse during the ovulatory phase—that is, when the estrogen level is high (9, 10). Because hormone levels in general are under strong genetic influences (11, 12), these relationships between hormone levels and behavior suggest one possible channel for the intergenerational transmission of behavior.

Because men and women have sharply different levels of sex hormones, it is natural to think that hormones are implied in the differences between male and female behavior. Experimental evidence shows that, on average, women tend to be more risk averse, less competitive, and more prosocial than men (13). Hormones affect the brain by binding to specific receptors, and previous work suggests that differences in the organization of brain areas in males and females depend on hormones (14–16). Hormones may affect cognition, mood, well-being, sexuality, and social behavior (16–19).

However, the existing evidence on the relationship between sex hormones and economic behavior is merely correlative. It does not admit causal inference. To investigate whether there is a causal link, we conducted a double-blind randomized trial, with subjects randomly allocated to treatments with estrogen, testosterone, or placebo (Fig. 1). The subjects were healthy postmenopausal women in the 50–65 year age group, carefully screened to rule out any contraindications to treatment. After 4 weeks of treatment the subjects participated in a series of economic experiments with real monetary payoffs at the Karolinska University Hospital in Stockholm.

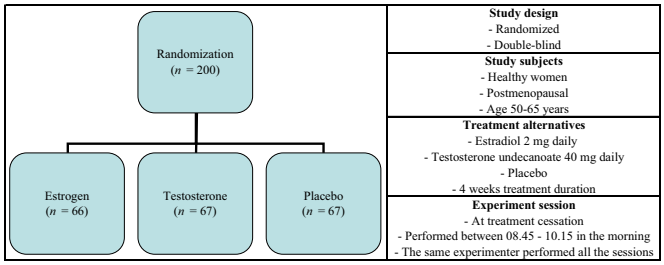

Fig. 1. An economic experiment based on a double-blind randomized trial. Two hundred subjects completed the study; 3 subjects initially randomly assigned did not complete the study (2 in the estrogen group and 1 in the placebo group).

To measure financial risk aversion (20), we elicited subjects' value of a 50/50 gamble to win Swedish Kronor (SEK) 400. This choice-based measure was complemented by two hypothetical questions used and validated by Dohmen et al. (1)—a hypothetical financial investment question (''risk investment'') and a survey question about the general willingness to take risks (''risk assessment''). We used a dictator game to measure subjects' altruism (21), an ultimatum game to measure their reciprocal fairness (22, 23), and a trust game to measure their trust and trustworthiness (24).

In comparison with placebo, we hypothesized that testosterone decreases risk aversion, altruism, trust, and trustworthiness and increases reciprocal fairness, and that estrogen increases risk aversion, altruism, trust, and trustworthiness and decreases reciprocal fairness.

Results

As illustrated in Fig. 2, the level of serum concentrations of estrogen and total and free testosterone increased significantly after 4 weeks of treatment compared with placebo (Mann–Whitney U test, $P < 0.001$, 2-sided). The mean total and free testosterone levels after 4 weeks of treatment were, respectively, 4.4 and 5.5 times higher than the mean baseline level in the testosterone group. In the estrogen group the mean estradiol

Author contributions: N.Z., L.K.-M., T.E., B.v.S., A.L.H., and M.J. designed research, performed research, analyzed data, and wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

Freely available online through the PNAS open access option.

[1]To whom correspondence should be addressed. E-mail: magnus.johannesson@hhs.se.

This article contains supporting information online at www.pnas.org/cgi/content/full/0812757106/DCSupplemental.

ECONOMIC SCIENCES

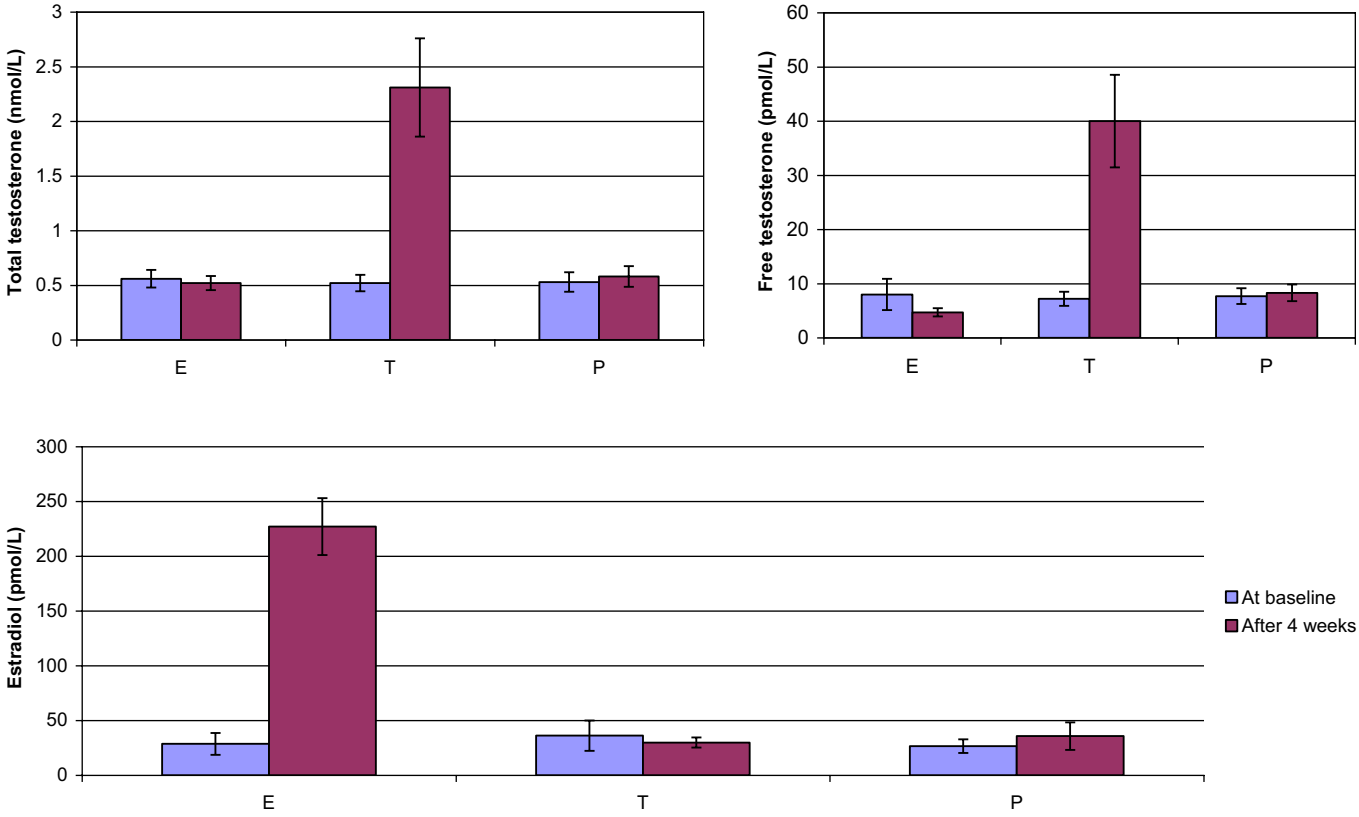

Fig. 2. Mean value of serum concentration of total (nmol/L) and free testosterone (pmol/L) and estradiol (pmol/L) at baseline and 4 weeks after treatments with estrogen (E), testosterone (T) and placebo (P). Error bars indicate 95% confidence intervals.

level increased by a factor of 7.9 after 4 weeks of treatment compared with baseline.

The main results of the study are summarized in Figs. 3 and 4. Contrary to our hypotheses, there were no significant differences between the 3 treatment groups for any of the studied economic behaviors (Mann–Whitney U test, $P > 0.05$ for all pairwise comparisons, 2-sided). There is considerable heterogeneity both in the increase in testosterone in the testosterone group (range, 0–10.15 nmol/L; SD, 1.84 nmol/L) and in the increase in estradiol in the estrogen group (range, −1–594.5 pmol/L; SD, 103.5 pmol/L). We therefore also tested whether the size of the increase, in the respective treatment group, was correlated with economic behavior. None of these correlations were significant (Spearman correlation, $P > 0.05$, 2-sided), further supporting the conclusion that sex hormones have no significant impact on economic behavior (see supporting information (SI) Table S1–S3 and Figs. S1–S2).

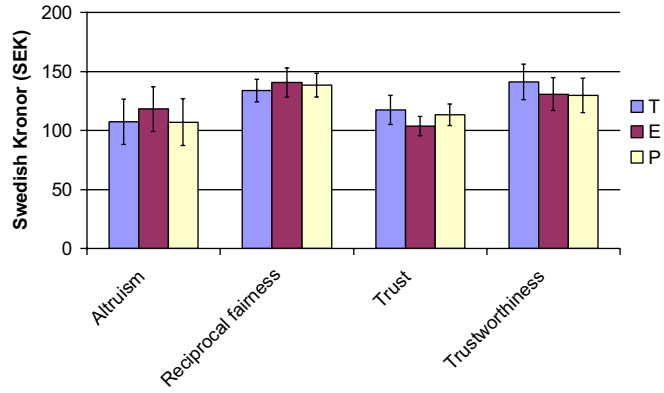

Fig. 3. Mean values of *altruism* (the amount donated to charity in the dictator game), *reciprocal fairness* (the acceptance threshold in the ultimatum game), *trust* (the amount of money invested in the trust game), and *trustworthiness* (the backtransfer in the trust game) after 4 weeks of treatments with testosterone (T), estrogen (E), and placebo (P). Error bars indicate 95% confidence intervals. There are no significant differences between any of the treatment groups (Mann–Whitney U test, $P > 0.05$, 2-sided).

Discussion

The induced changes in estrogen and testosterone levels have previously been associated with important clinical effects. Numerous studies support that estrogen therapy of this kind is effective for treatment of menopausal symptoms, such as flushing, sweating, and sleep disturbance (25). Furthermore, testosterone therapy resulting in similar serum levels as in this study has been shown to improve psychosexual function, e.g., arousal, desire, satisfaction, and well-being in postmenopausal women (19, 26, 27). Yet, our study offers no support for the hypothesis that sex hormones affect economic behavior.

Although a larger sample size is always desirable, our sample size is large compared with Kosfeld et al. (6). They found an effect of the hormone oxytocin on trust by using a sample size of 29 in each of 2 randomization groups. Our sample size in each of the 3 randomization groups is more than twice as large, giving us a considerably greater statistical power to detect differences in trust. It should furthermore be noted that the point estimates of differences in economic behavior between the groups are small, and often not consistent with our prior hypotheses.

The estimated relationship between testosterone and financial risk taking in Apicella et al. (8) can be used to illustrate the statistical power in our study. Their results imply that a doubling

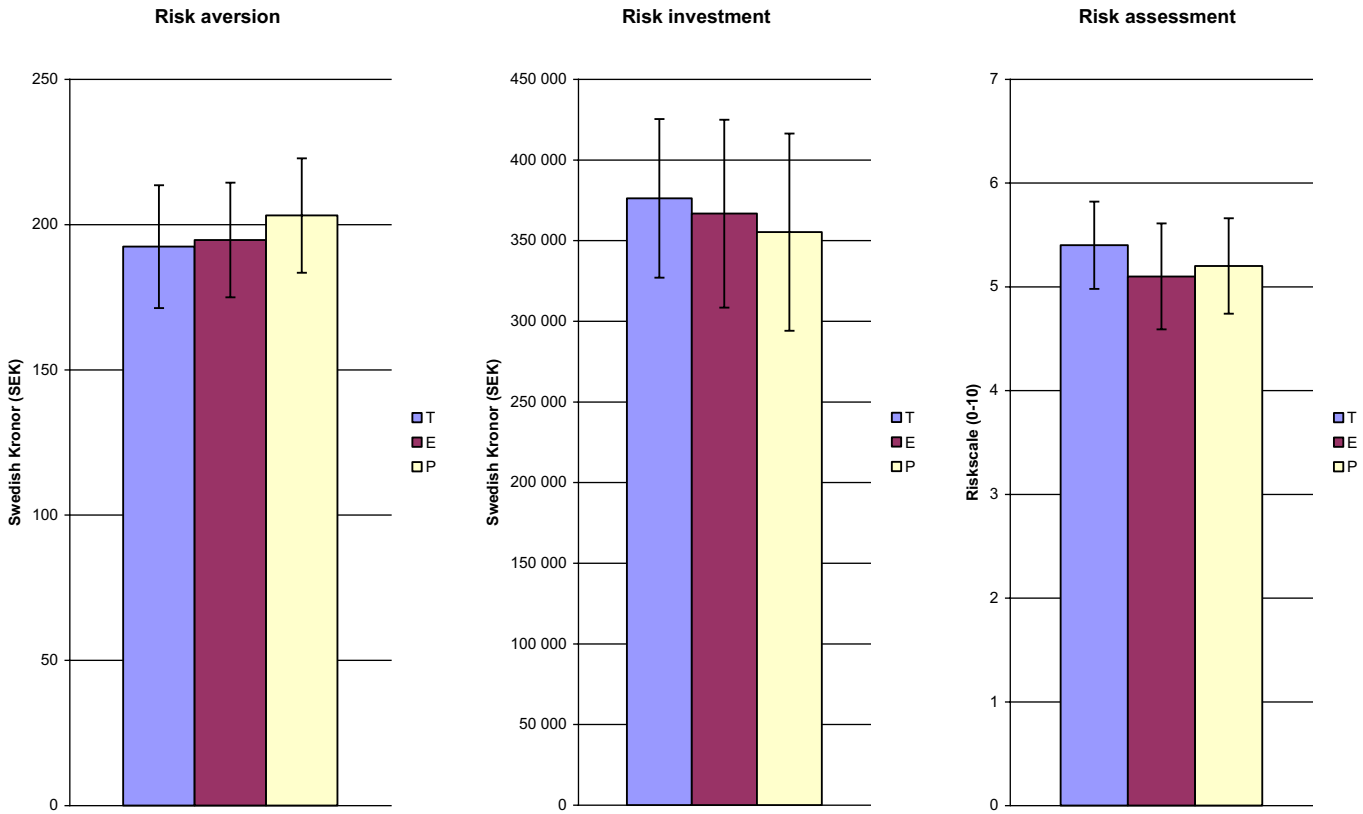

Fig. 4. Mean values of *risk aversion* (the certainty equivalent to a 50/50 gamble to win SEK 400), *risk investment* (the amount of money hypothetically invested in a profitable but risky investment), and *risk assessment* (the general willingness to take risks on a 0–10 scale), after 4 weeks of treatments with testosterone (T), estrogen (E), and placebo (P). Error bars indicate 95% confidence intervals. There are no significant differences between any of the treatment groups (Mann–Whitney *U* test, $P > 0.05$, 2-sided).

of the testosterone level increases risk taking by 39%. The statistical power in our study to detect a difference of this magnitude at the 5% significance level is well >90% for all of our 3 measures of risk taking (based on the means and standard deviations of the risk measures in our sample). Note also that, rather than doubling the testosterone level as implied in the power estimations above, the increase in testosterone in our study was more than 4-fold.

The few previous studies suggesting an influence of testosterone on economic behavior were all obtained in men and based on correlation analysis of endogenous hormone levels (7, 8). Quantification of unbound bioactive testosterone is complex and available commercial assays are inconsistent. Recently, calculation based on the law of mass action, as used in the present study, was found to be a more reliable method than measurement in salivary samples (28).

The findings in the present trial do not rule out that early exposure to sex hormones could affect economic behavior. Congenital adrenal hyperplasia (CAH) is a rare genetic condition of androgen excess during embryonic development that seems to influence behavior later in life. Although treatment normalizes hormone levels, girls with CAH are reported to exhibit more boy-typical play behavior and to have better spatial abilities than controls (29, 30). However, the underlying mechanisms for such effects are not known.

We conclude that the correlation between economic behavior and estrogen and testosterone found in previous studies may occur because these sex hormones are in turn correlated with other biological factors causally linked to economic behavior. Alternatively, the previous results are spurious, with the lack of countervailing evidence being due to publication bias (31).

Materials and Methods

Approval. The study was approved by the local ethics committee in Stockholm (2006/481-31/3) and the Swedish Medical Products Agency (151:2006/29773) and all women gave their written consent to participate in the study.

Recruitment and Study Outline. The study was carried out at the Women's Health Research Unit at the Karolinska University Hospital, Stockholm, Sweden. Women were mainly recruited based on advertisements in newspapers. An initial screening was made based on a first contact by phone. Subjects that passed the initial screening participated in a comprehensive screening visit at the Karolinska University Hospital consisting of a medical and gynecological examination ($n = 240$). Subjects that fulfilled the inclusion criteria, detailed below, were then randomized to 1 of 3 treatment groups ($n = 203$). The subjects received the tablets during a second morning visit to the Women's Health Research Unit, where blood samples also were taken after an overnight fast. Serum was separated by centrifugation and then stored at −70 °C for later analysis of sex hormones.

Each subject was randomly assigned to estrogen (Estradiol, 2 mg/day), testosterone (Testosterone undecanoate, 40 mg/day), or placebo treatment for a period of 4 weeks. The randomization was carried out with blocks of 4 and 12 subjects in each block. The study medication was tested and manufactured by the National Corporation of Swedish Pharmacies in identical capsules. At a third visit, the first morning after the cessation of therapy, a new blood sample was taken after an overnight fast. After receiving breakfast at the clinic, each woman (in groups of 1–6 individuals) participated in an experimental session that took ≈1.5 h ($n = 200$ completed the study). All experimental sessions in the study were conducted by the same person and between 0845 and 1015 in the morning. The experimental sessions were carried out between March 2007 and June 2008.

Inclusion and Exclusion Criteria. Healthy naturally postmenopausal women in the 50–65 year age group with body mass index (BMI) 19–30 were recruited into the study. Postmenopausal status was defined as last menstrual bleeding at least 12 months before beginning the study or serum levels of follicle-

stimulating hormone (FSH) >30 IU/L. Exclusion criteria were smoking, hypertension, hyperlipidemia, or other cardiovascular disease, risk factors for thromboembolism, diabetes, and history of cancer. Intake of any sex steroid hormones during the past 3 months was not allowed. However, well-controlled thyroid hormone substitution for treatment of hypothyroidism was permitted.

Laboratory Tests. Serum concentrations of total testosterone and estradiol were determined by radioimmunoassay by using commercial kits from Diagnostic Products Corporation (DPC) (Coat-a-Count , testosterone), and from Orion Diagnostica (Spectria , estradiol). Serum concentrations of sex hormone-binding globulin (SHBG) and FSH were determined by chemiluminescent enzyme immunometric assays (IMMULITE, Diagnostic Products). Detection limits and intra-assay and interassay coefficients of variation were 0.2 nmol/L, 6% and 11% for testosterone; 5 pmol/L, 7% and 10% for estradiol; 0.2 nmol/L, 7% and 13% for SHBG; and 0.1 IU/L, 5% and 8% for FSH. Apparent concentrations of free testosterone were calculated from values of total testosterone, SHBG, and a fixed albumin concentration of 40 g/L by successive approximation with a computer program based on an equation system derived from the law of mass action (32).

Economic Experiments. The monetary stakes in the experiments were sizeable, and on average a subject earned SEK 1,050 (approximately $150; exchange rate at the time of the study; $1 = SEK 6.5). In some of the experiments a subject was randomly matched with another anonymous subject. Subjects were never matched with the same counterpart more than once.

A modified dictator game was used to measure altruistic behavior (21). Each subject decided how to allocate SEK 200 between herself and a charitable organization (a charity called ''Stadsmissionen,'' which predominantly focuses on helping the homeless in Sweden). The size of the donation is our measure of altruism.

The second and third experiment concerned ultimatum game behavior (22). The ultimatum game is a 2-person game in which one subject proposes how to split a sum of money and the other subject can accept or reject the proposal. If the proposal is accepted, the money is split according to the proposal; otherwise, neither subject gets any money. In the proposer role (second experiment), subjects propose a division of SEK 400 between themselves and an anonymous counterpart (only proposals in even SEK 50 increments were allowed). Because 92% of the subjects proposed a 50/50 split, there is no scope for finding an effect on sex hormones on proposals in the ultimatum game. The same strong tendency toward a 50/50 split was also found in a previous study on Swedish twins (3). In the third experiment, subjects played the role of an ultimatum game responder. We used the so-called strategy method (2) to elicit the acceptance threshold in the ultimatum game, with each subject determining whether she would accept or reject every possible proposal (in multiples of SEK 50) before learning the actual proposal. The acceptance threshold for each individual is defined as the midpoint of the lowest offer accepted and the previous offer. All subjects exhibited monotonic acceptance behavior in the range of offers between 0% and 50%. The acceptance threshold is our measure of ''reciprocal fairness'' (23).

The fourth and fifth experiment concerned trust game behavior (24). A trust game is a 2-player game in which one player, the trustor, decides how much of an endowment to invest. The investment is multiplied by 3, whereon the other player, the trustee, decides how to allocate the resulting amount between herself and the trustor. In the fourth experiment, each subject played the trustor role, deciding how much money out of an initial endowment of SEK 150 to send to a randomly selected anonymous counterpart. In the fifth experiment, each subject played the role of trustee, deciding how much to send back to the investor for every possible investment (SEK 50, 100, and 150), before learning the actual investment. The investment in the first stage is our measure of ''trust.'' The average back transfer (in SEK) for the 3 possible investment levels is our measure of ''trustworthiness.''

The final experiment with real monetary stakes measured the subjects' risk aversion. Each subject made 6 choices between a certain payoff and a 50/50 gamble to win SEK 400 (20). The certain payoffs were set to SEK 80, 120, 160, 200, 240, and 300. After the subjects had made their 6 choices, one of the choices was randomly chosen for payoff by rolling a die. The gamble was resolved by a coin toss in front of the subjects. The experiment determines 7 intervals for the certainty equivalent and the certainty equivalent was set to the midpoint of the interval. All subjects made monotonic choices. The certainty equivalent is our measure of ''risk aversion.''

The subjects also filled out a questionnaire with 2 hypothetical questions about risk attitudes. The first question asks the subject to imagine that she has won SEK 1 million on the lottery and that she can invest some of this money in a risky asset with an equal probability of doubling the investment and losing half the investment (1). Subjects can choose between 6 levels of investments: SEK 0, 200,000, 400,000, 600,000, 800,000, and 1,000,000. The investment is our measure of ''risk investment.'' The second question measures general risk attitudes on a 0 to 10 scale, where 0 is complete unwillingness to take risks and 10 is complete willingness to take risks (1). The scale value is our measure of ''risk assessment.'' In line with the results of Dohmen et al. (1), the 3 risk attitude measures in our study are all significantly correlated with each other (Spearman correlation, $P < 0.05$, 2-sided).

ACKNOWLEDGMENTS. This work was supported by the Jan Wallander and Tom Hedelius Foundation, The Swedish Council for Working Life and Social Research, The Swedish Research Council, and the Karolinska Institutet.

1. Dohmen T, et al. (2005) *Individual Risk Attitudes: New Evidence From a Large, Representative, Experimentally Validated Survey* (Institute for the Study of Labor Discussion Paper no. 1730, Bonn, Germany).
2. Camerer CF (2003) *Behavioral Game Theory* (Princeton Univ Press, Princeton, NJ).
3. Wallace B, Cesarini D, Lichtenstein P, Johannesson M (2007) Heritability of ultimatum game responder behavior. *Proc Natl Acad Sci USA* 104:15631–15634.
4. Cesarini D, et al. (2008) Heritability of cooperative behavior in the trust game. *Proc Natl Acad Sci USA* 105:3721–3726.
5. Cesarini D, Dawes CT, Johannesson M, Lichtenstein P, Wallace B (2009) Genetic variation in preferences for giving and risk-taking. *Q J Econ*, in press.
6. Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E (2005) Oxytocin increases trust in humans. *Nature* 435:673–676.
7. Burnham TC (2007) High-testosterone men reject low ultimatum game offers. *Proc R Soc B* 274:2327–2330.
8. Apicella CL, et al. (2008) Testosterone and financial risk preferences. *Evol Hum Behav* 29:384–390.
9. Chavanne TJ, Gallup GG (1998) Variation in risk taking behavior among female college students as a function of the menstrual cycle. *Evol Hum Behav* 19:27–32.
10. Bröder A, Hohmann N (2003) Variations in risk taking behavior over the menstrual cycle: An improved replication. *Evol Hum Behav* 24:391–398.
11. Harris JA, Vernon PA, Boomsma DI (1998) The heritability of testosterone: A study of Dutch adolescent twins and their parents. *Behav Genet* 28:165–171.
12. Bartels M, Van den Berg SM, Sluyter F, Boomsma DI, de Geus EJC (2003) Heritability of cortisol levels: Review and simultaneous analysis of twin studies. *Psychoneuroendocrino* 28:121–137.
13. Croson R, Gneezy U, Gender differences in preferences. *J Econ Lit*, in press.
14. Genazzani AR, Monteleone P, Gambacciani M (2002) Hormonal influence on the central nervous system. *Maturitas* 43:11–17.
15. McEwen B (2002) Estrogen actions throughout the brain. *Recent Prog Horm Res* 57:357–384.
16. Genazzani AR, Pluchino N, Luisi S, Luisi M (2007) Estrogen, cognition and female ageing. *Hum Reprod Update* 13:175–187.
17. Sherwin BB (1998) Affective changes with estrogen and androgen replacement therapy in surgically menopausal women. *J Affect Disorders* 14:177–187.
18. Davis SR, Tran J (2001) Testosterone influences libido and well-being in women. *Trends Endocrinol Metab* 12:33–37.
19. Davis SR, et al. (2008) Testosterone for low libido in menopausal women not taking estrogen therapy. *N Engl J Med* 359:2005–2017.
20. Holt CA, Laury SK (2002) Risk aversion and incentive effects. *Am Econ Rev* 92:1644–1655.
21. Eckel C, Grossman P (1996) Altruism in anonymous dictator games. *Game Econ Behav* 16:181–191.
22. Guth W, Schmittberger R, Schwarze B (1982) An experimental analysis of ultimatum bargaining. *J Econ Behav Organ* 3:367–388.
23. Knoch D, Pascual-Leone A, Meyer K, Treyer V, Fehr E (2006) Diminishing reciprocal fairness by disrupting the right prefrontal cortex. *Science* 314:829–832.
24. Berg JE, Dickhaut J, McCabe K (1995) Trust, reciprocity, and social history. *Game Econ Behav* 10:122–142.
25. Utian WH, et al. (2008) Estrogen and progestogen use in postmenopausal women: July 2008 position statement of the North American Menopause Society. *Menopause* 15:584–602.
26. Flöter A, Nathorst-Böös J, Carlström K, von Schoultz B (2002) Addition of testosterone to estrogen replacement therapy in oophorectomized women: Effects on sexuality and well-being. *Climacteric* 5:357–365.
27. Shifren JL, et al. (2000) Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med* 343:682–688.
28. Miller KK, et al. (2004) Measurement of free testosterone in normal women and women with androgen deficiency: Comparison of methods. *J Clin Endocrinol Metab* 89:525–533.
29. Nordenström A, Servin A, Bohlin G, Larsson A, Wedell A (2002) Sex-typed toy play behavior correlates with the degree of prenatal androgen exposure assessed by CYP21 genotype in girls with congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 87:5119–5124.
30. Hampson E, Rovet JF, Altmann D (1998) Spatial reasoning in children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Dev Neuropsychol* 14:299–320.
31. Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR (1991) Publication bias in clinical research. *Lancet* 337:867–872.
32. Södergard R, Bäckström T, Shanbhag V, Carstensen H (1982) Calculation of free and bound fractions of testosterone and estradiol-17β to human plasma proteins at body temperature. *J Steroid Biochem* 16:801–810.